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EDITORIAL COMMENT

T_1 Mapping for Diffuse Myocardial Fibrosis

A Key Biomarker in Cardiac Disease?*

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Multicellular organisms are built of cells embedded in the interstitium, the scaffolding of organs and tissues. In disease, the ratio between cells and interstitium changes due to interstitial expansion as a result of increased collagen (focal and diffuse fibrosis) or accumulation of exogenous material such as amyloid. In most organs and diseases (e.g., liver cirrhosis), diffuse fibrosis plays a key role, and fibrosis quantification guides therapy. In the heart, diffuse fibrosis appears histologically ubiquitous, but it remains clinically invisible, and the gold standard test, invasive myocardial biopsy, has significant morbidity and sampling error. Cardiovascular magnetic resonance measures focal fibrosis (scar) by using late gadolinium enhancement, but this method is unable to quantify diffuse fibrosis. T_1 mapping, a new cardiovascular magnetic resonance technique, can now noninvasively quantify the myocardial extracellular volume (ECV), reflecting diffuse fibrosis (1).

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The longitudinal relaxation time (T_1) of a tissue indicates how rapidly protons recover after a radiofrequency pulse. Pre-contrast (native) T_1 varies with water content and may increase in cases of diffuse myocardial fibrosis (2), but it inherently embodies composite signal from both cells and interstitium, and it varies with measurement technique and magnetic resonance imaging field strength. After extracellular gadolinium-based contrast administration, T_1 is dominated by and is inversely proportional to the concentration of gadolinium. Measuring T_1 after contrast provides a value linked to the interstitium, but post-contrast T_1 also varies due to gadolinium dose, clearance rate, time post bolus, body composition, and hematocrit. If the change in T_1 pre-contrast and post-contrast is measured in both blood and myocardium after equilibration of the contrast distribution, the partition coefficient can be calculated. By correcting for the hematocrit level, the myocardial ECV is derived, which is a more stable and biologically significant biomarker. The utility of ECV measurement is increasingly being reported across the spectrum of cardiology (3), and new data show ECV, in unselected patients, predicts outcomes at least as strongly as left ventricular ejection fraction (4,5).

In this issue of the *Journal*, Liu et al. (6) present a large cohort, based on CMR data from 1,231 participants aged 54 to 93 years from the Multi-Ethnic Study of Atherosclerosis (MESA) study, and investigated the relationship between CMR indices and age/sex. The authors are congratulated for integrating T_1 measurement into the MESA study, providing data on normal ranges, mechanisms of sex differences, and correlations with clinical findings from this well-characterized cohort. Previously, only small, single-center studies have demonstrated a correlation between ECV and age (3). The authors used a single breath-hold Modified Look-Locker Inversion recovery (MOLLI) (7) sequence in one mid short axis slice, showing that women had significantly higher pre-contrast T_1 times and partition coefficient as well as lower post-contrast T_1 times than men. When hematocrit data were available, ECV was higher in women than in men (28.1 ± 2.8% vs. 25.8 ± 2.9%; $p < 0.001$). Using multivariable linear regression, ECV increased with age in men with every decade ($p < 0.001$), but in women, ECV decreased with age. In the overall cohort, ECV was correlated with age ($R^2 = 0.021$; $p = 0.012$).

What are we to make of these results? At face value, they may explain some sex differences in the prevalence of congestive heart failure (8) and support the idea that diffuse myocardial fibrosis increases with age. However, unresolved questions remain. Age and ECV correlated weakly, with an R^2 of only 0.021, meaning that 97.9% of all ECV variation is explained by factors other than age. Although the age–ECV relation was statistically significant, the clinical significance is less certain. In fact, one could reasonably conclude, that because age is so minimally related to myocardial fibrosis, most people can age successfully without inexorable, age-related myocardial fibrosis—an optimistic interpretation indeed. Second, risk adjustment addressed the presence of comorbidities but not their severity. Disease severity, including longer "exposure" to comorbidity (e.g., hypertension), may increase with age and introduce residual confounding not addressed by the statistical modeling. Third, the sex-related results may be confounded by menopause.

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From a technical perspective, the T_1 mapping field is rapidly advancing. The iteration of the Modified Look-Locker Inversion recovery (MOLLI) sequence used in this study (6) has improved. Single breath-hold mapping (in which each pixel carries the T_1 value) has replaced multi breath-hold methods, and newer refinements include iterative reconstruction, shorter breath-holds, better sequence design, and, lately, ECV maps with pixel-by-pixel representation of ECV for a simplified detection, measurement and quantitative display of diffuse fibrosis (9). There is an apparent spectrum of interstitial expansion with cardiac amyloid, aortic stenosis, and cardiomyopathy having large changes in ECV; age and sex, however, have much smaller or possibly no contributions (10). The ratio of pathophysiological signal to measurement error determines test performance. T_1 mapping seems especially robust in detecting disease characterized by high ECV, such as amyloid (in which the ECV is often >0.5) (11) or marked native T_1 contrast diseases such as Anderson-Fabry disease (in which fat storage makes native T_1 fall) (12).

The field of T_1 mapping and noninvasive fibrosis quantification faces the same challenges as any other new technology. A key task will be to let the energy and creative chaos of early development and competing methodologies (e.g., different scanner manufacturers, contrast agents, field strengths, T_1 mapping sequences) transition through collaboration into more standardized methodologies sufficient for use to: diagnose disease; define mechanistic pathways of disease affecting the interstitium, the myocyte, or both; change therapy; and use ECV as a surrogate endpoint in trials of drug development, an aim underpinning the recently formed T_1 mapping development group.

Ultimately, ECV diffuse fibrosis measures could dramatically affect cardiology. We can now dichotomize the myocardium into its cellular and interstitial components, and advance understanding of disease mechanisms and their relative contribution to cardiac vulnerability, which are critically important issues. More data demonstrating fibrosis as a therapeutic target are needed, but because fibrosis guides research and patient management in liver and lung disease, the same principles may apply to the heart. Conceivably, T_1 mapping for ECV could facilitate drug development and guide therapy, especially in the setting of heart failure, in which drug development strategies have produced few positive results over the last decade (13). Exciting times are ahead. Cardiac fibrosis promises to be as fundamental as fibrosis elsewhere. Its measurement may define disease, predict outcome, determine the choice and timing of interventions, enhance drug development, and be more treatable.

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REFERENCES

1. White SK, Sado DM, Flett AS, Moon JC. Characterising the myocardial interstitial space: the clinical relevance of non-invasive imaging. Heart 2012;98:773–9.
2. Bull S, White SK, Piechnik SK, et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart 2013;99:932–7.
3. Ugander M, Oki AJ, Hsu LY, et al. Extracellular volume imaging by magnetic resonance imaging provides insights into overt and subclinical myocardial pathology. Eur Heart J 2012;33:1268–78.
4. Wong TC, Piehler K, Meier CG, et al. Association between extracellular matrix expansion quantified by cardiovascular magnetic resonance and short-term mortality. Circulation 2012;126:1206–16.
5. Wong TC, Piehler K, Kang IA, et al. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. Eur Heart J 2013 Jun 11 [E-pub ahead of print]. http://dx.doi.org/10.1093/eurheartj/eht193.
6. Liu CY, Liu Y-C, Wu C, et al. Evaluation of Age-Related Interstitial Myocardial Fibrosis With Cardiac Magnetic Resonance Contrast-Enhanced T_1 Mapping: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2013;62:1280–7.
7. Messroghli DR, Walters K, Plein S, et al. Myocardial T1 mapping: application to patients with acute and chronic myocardial infarction. Magn Reson Med 2007;58:34–40.
8. Ceia F, Fonseca C, Mota T, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail 2002;4:531–9.
9. Kellman P, Wilson JR, Xue H, Ugander M, Arai AE. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. J Cardiovasc Magn Reson 2012;14:63.
10. Sado DM, Flett AS, Banypersad SM, et al. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. Heart 2012;98:1436–41.
11. Karamitsos TD, Piechnik SK, Banypersad SM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. J Am Coll Cardiol Img 2013;6:488–97.
12. Sado DM, White SK, Piechnik SK, et al. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. Circ Cardiovasc Imaging 2013;6:392–8.
13. Butler J, Fonarow GC, Gheorghiade M. Strategies and opportunities for drug development in heart failure. JAMA 2013;309:1593–4.

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